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Whole genome sequence association analysis of Brain MRI measures

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Abstract

Background: Genome-wide association studies (GWAS) of brain volumes have identified common genetic variants with modest effect sizes that lie mainly in non-coding regions. We sought to identify low frequency and rare variants influencing brain volumes by performing association analyses using whole-genome sequence data from the Trans-Omics for Precision Medicine (TOPMed) Program.

Method: We analyzed up to 7,607 participants (57% women; 62% European ancestry, 21% African-Americans, 15% Hispanic/Latino, 2% Chinese-American), mean age of 60.5 (16.2), from eight TOPMed population- or family-based studies (FHS, GENESTAR, CHS, GENOA, ARIC, CARDIA, MESA, and SAFS). We excluded participants with dementia, stroke, presence of large brain infarcts, tumor or low-quality scans. We tested the association of hippocampal (HV), total brain (TBV), lateral ventricular (LVV) and intracranial (ICV) volumes to individual genetic variants with minor allele counts ≥ 15 using mixed-effect linear regression models adjusted for age, age^2, sex, study and the first 10 principal components. Models for HV, TBV and log(LVV) were adjusted for ICV. We accounted for relatedness using an empirical kinship matrix and trait variance variability by using a random effect for study.

Result: We detected one novel region with low frequency variants associated with HV (13q14, P = 5.8×10^{-9}). The top 13q14 variant for HV (rs115674829) minor allele frequency (MAF) was 2% in our pooled sample but was more common in the pan-African 1000 Genomes population (MAF = 14%). This variant lies in *LINC00598* at 237kb from *FOXO1*, a member of the forkhead family of transcription factors that has been linked to

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Alzheimer's Disease. Additionally, we detected new suggestive associations ($P \leq 10^{-7}$) for TBV (16p11) and LVV (1q25, 2q22, 3q13, 5q14, and 10q23), including common variants. Finally, we confirmed the association of common variants in GWAS loci for all traits.

Conclusion: Our whole genome sequence analyses revealed intriguing new loci of low-frequency and common variants, and replicated loci previously associated with brain volumes. Future work will include ancestry-specific and conditional analyses, as well as gene-based and scan tests.
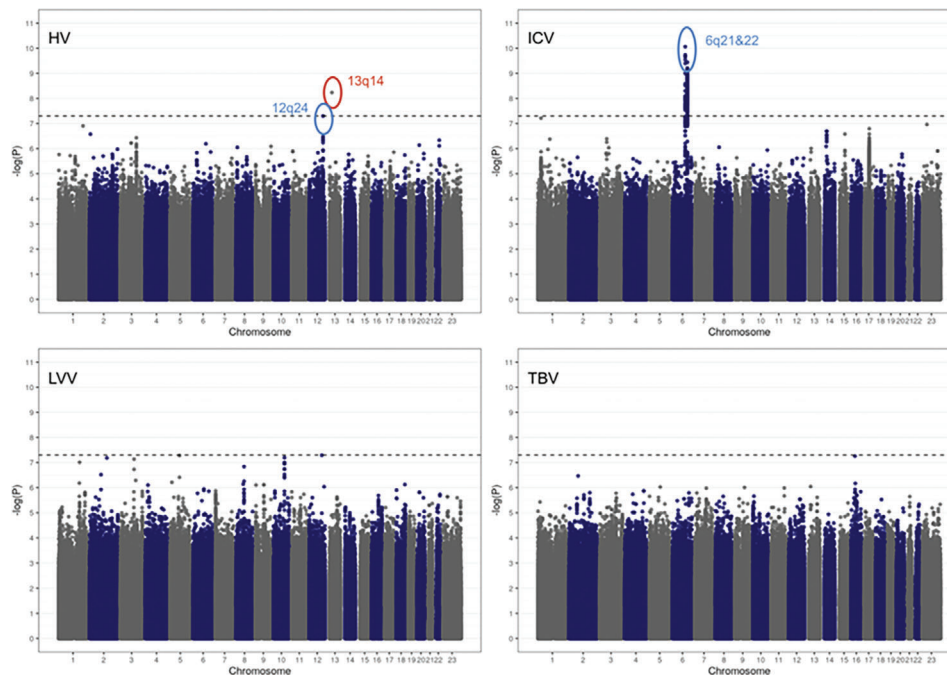
Figure 1: Manhattan Plots for Brain MRI Volumes Based on TOPMed Whole-Genome Sequence Association Analysis. Dotted line demarkates genome-wide significance ($P \leq 5 \times 10^{-8}$). RED annotations indicate novel significant loci, while BLUE annotations indicate replicated significant loci. HV = hippocampal volume; ICV = intracranial volume; LVV = log lateral ventricular volume; TBV = total brain volume.

Table 1: Novel Brain MRI Volumes Association Results Based on TOPMed Whole-Genome Sequence Association Analysis

Location	EAF	EA/NEA	Effect	P-value	rsID	Trait
1q25	0.2684	T/C	-0.039	9.7e-08	rs3795503	LVV
2q22	0.0011	C/G	0.564	6.5e-08	rs187704649	LVV
3q13	0.0011	G/A	0.527	7.3e-08	rs565601707	LVV
5q14	0.2730	T/C	0.039	5.2e-08	rs78861128	LVV
10q23	0.4254	A/G	-0.036	6.4e-08	rs2068888	LVV
13q14	0.0217	A/G	-0.264	5.8e-09	rs115674829	HV
16p11	0.0011	G/A	49.811	5.5e-08	rs971709419	TBV

EAF = Effect allele frequency; EA = effect allele; NEA = non-effect allele; LVV = log lateral ventricular volume; HV = hippocampal volume; TBV = total brain volume.

Table 2: Confirmation of Brain MRI Volumes GWAS Loci Based on TOPMed Whole-Genome Sequence Association Analysis

Location	EAF	EA/NEA	Effect	P-value	rsID	Trait
3q28	0.347	A/G	-0.033	2.2e-06	rs34113929	LVV
10p12	0.244	A/T	-0.019	0.015	rs35587371	LVV
11q23	0.316	G/A	-0.024	0.00044	rs7936534	LVV
12q23	0.067	C/T	0.071	5.1e-08	rs12146713	LVV
16q24	0.533	A/G	0.028	3.2e-05	rs9937293	LVV
22q13	0.553	A/C	-0.018	0.0079	rs4820299	LVV
5q12	0.345	T/G	-0.034	0.0051	rs2289881	HV
9q33	0.370	C/G	0.037	0.0027	rs7020341	HV
12q14	0.118	G/T	-0.059	0.0011	rs61921502	HV
12q24	0.082	T/C	0.11	5.0e-08	rs146607495	HV
2q32	0.098	A/G	-2.11	0.024	rs288326	TBV
6q21	0.559	T/C	1.34	0.027	rs2764264	TBV
17q21	0.166	G/A	-2.34	0.0016	rs62057149	TBV
3q28	0.049	C/G	10.8	0.0052	rs9811910	ICV
6q21	0.470	-/C	-12	8.6e-11	rs35947181	ICV
6q22	0.49	T/C	11	3.6e-10	rs1490384	ICV
10q24	0.275	T/G	3.3	0.085	rs11191683	ICV
12q14	0.571	T/A	-6.1	0.00042	rs138074335	ICV
12q23	0.185	C/G	-6.6	0.0024	rs2195243	ICV
17q21	0.156	G/T	-10.6	6.4e-06	rs199525	ICV